

17437CON2(AP)

**EP₄ AGONISTS AS AGENTS FOR LOWERING INTRAOCULAR
PRESSURE**

5 **CROSS REFERENCE TO RELATED APPLICATIONS**

This patent application is a continuation of 10/346,828, filed January 16, 2003, which is a continuation in part of Serial No. 09/882,720, filed June 14, 2001.

10 **Field of the Invention**

The present invention relates to EP₄ agonists, for example 3, 7 or 3 and 7 thia or oxa prostanoid acid derivatives as potent ocular hypotensives that are particularly suited for the management of glaucoma.

15 **Background of the Invention**

Description of Related Art

20 Ocular hypotensive agents are useful in the treatment of a number of various ocular hypertensive conditions, such as post-surgical and post-laser trabeculectomy ocular hypertensive episodes, glaucoma, and as presurgical adjuncts.

 Glaucoma is a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, glaucoma has been classified as primary or
25 secondary. For example, primary glaucoma in adults (congenital glaucoma) may be either open-angle or acute or chronic angle-closure. Secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged cataract.

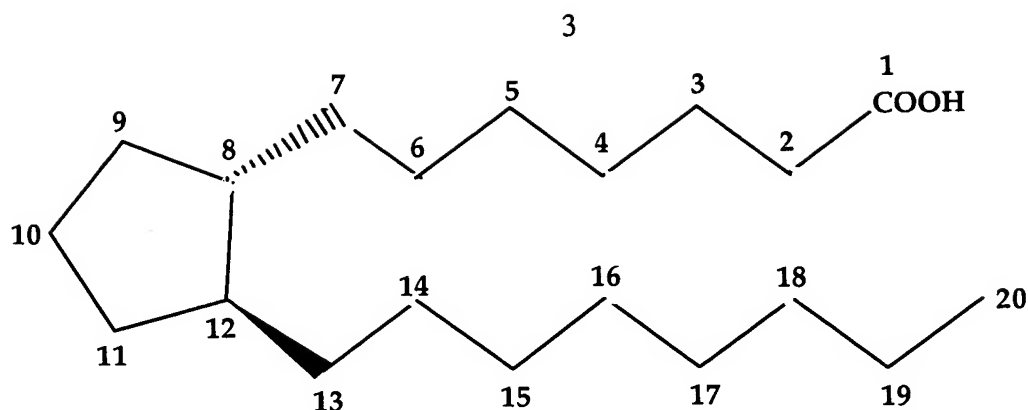
 The underlying causes of primary glaucoma are not yet known. The increased intraocular tension is due to the obstruction of aqueous humor outflow. In
30 chronic open-angle glaucoma, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute or chronic

angle-closure glaucoma, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the entrance of the canal of Schlemm. Dilation of the pupil may push the root of the iris forward against the angle, and may produce pupillary block and thus precipitate an acute attack. Eyes
5 with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.

Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior segment may prevent
10 aqueous escape by causing complete posterior synechia in iris bombe, and may plug the drainage channel with exudates. Other common causes are intraocular tumors, enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

Considering all types together, glaucoma occurs in about 2% of all persons
15 over the age of 40 and may be asymptotic for years before progressing to rapid loss of vision. In cases where surgery is not indicated, topical β -adrenoreceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

Certain eicosanoids and their derivatives have been reported to possess ocular hypotensive activity, and have been recommended for use in glaucoma management.
20 Eicosanoids and derivatives include numerous biologically important compounds such as prostaglandins and their derivatives. Prostaglandins can be described as derivatives of prostanoic acid which have the following structural formula:



Various types of prostaglandins are known, depending on the structure and substituents carried on the alicyclic ring of the prostanoic acid skeleton. Further classification is based on the number of unsaturated bonds in the side chain indicated by numerical subscripts after the generic type of prostaglandin [e.g. prostaglandin E₁ (PGE₁), prostaglandin E₂ (PGE₂)], and on the configuration of the substituents on the alicyclic ring indicated by α or β [e.g. prostaglandin F₂ α (PGF₂ β)].

Prostaglandins were earlier regarded as potent ocular hypertensives, however, evidence accumulated in the last decade shows that some prostaglandins are highly effective ocular hypotensive agents, and are ideally suited for the long-term medical management of glaucoma (see, for example, Bito, L.Z. Biological Protection with Prostaglandins, Cohen, M.M., ed., Boca Raton, Fla, CRC Press Inc., 1985, pp. 231-252; and Bito, L.Z., Applied Pharmacology in the Medical Treatment of Glaucomas Drance, S.M. and Neufeld, A.H. eds., New York, Grune & Stratton, 1984, pp. 477-505. Such prostaglandins include PGF₂ α , PGF₁ α , PGE₂, and certain lipid-soluble esters, such as C₁ to C₂ alkyl esters, e.g. 1-isopropyl ester, of such compounds.

Although the precise mechanism is not yet known experimental results indicate that the prostaglandin-induced reduction in intraocular pressure results from increased uveoscleral outflow [Nilsson et.al., Invest. Ophthalmol. Vis. Sci. (suppl), 284 (1987)].

The isopropyl ester of PGF₂ α has been shown to have significantly greater hypotensive potency than the parent compound, presumably as a result of its more

effective penetration through the cornea. In 1987, this compound was described as "the most potent ocular hypotensive agent ever reported" [see, for example, Bito, L.Z., Arch. Ophthalmol. 105, 1036 (1987), and Siebold et.al., Prodrug 5 3 (1989)].

Whereas prostaglandins appear to be devoid of significant intraocular side effects, ocular surface (conjunctival) hyperemia and foreign-body sensation have been consistently associated with the topical ocular use of such compounds, in particular PGF₂α and its prodrugs, e.g., its 1-isopropyl ester, in humans. The clinical potentials of prostaglandins in the management of conditions associated with increased ocular pressure, e.g. glaucoma are greatly limited by these side effects.

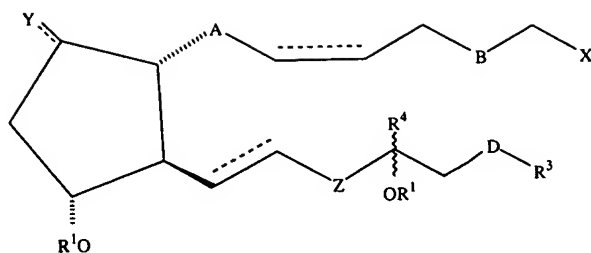
In a series of co-pending United States patent applications assigned to Allergan, Inc. prostaglandin esters with increased ocular hypotensive activity accompanied with no or substantially reduced side-effects are disclosed. The co-pending USSN 596,430 (filed 10 October 1990, now U.S. Patent 5,446,041), relates to certain 11-acyl-prostaglandins, such as 11-pivaloyl, 11-acetyl, 11-isobutyryl, 11-valeryl, and 11-isovaleryl PGF₂α. Intraocular pressure reducing 15-acyl prostaglandins are disclosed in the co-pending application USSN 175,476 (filed 29 December 1993). Similarly, 11,15- 9,15 and 9,11-diesters of prostaglandins, for example 11,15-dipivaloyl PGF₂α are known to have ocular hypotensive activity. See the co-pending patent applications USSN Nos. 385,645 (filed 07 July 1989, now U.S. Patent 4,994,274), 584,370 (filed 18 September 1990, now U.S. Patent 5,028,624) and 585,284 (filed 18 September 1990, now U.S. Patent 5,034,413). The disclosures of all of these patent applications are hereby expressly incorporated by reference.

Summary of the Invention

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The present invention concerns a method of treating ocular hypertension which comprises administering to a mammal having ocular hypertension a therapeutically effective amount of an EP₄ agonist, e.g. a compound of formula I

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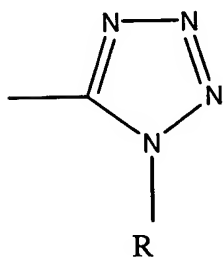
wherein hatched lines represent the α configuration, a triangle represents the β configuration, a wavy line represents either the α configuration or the β

- 5 configuration and a dotted line represents the presence or absence of a double bond;
A and B are independently selected from the group consisting of O, S and CH_2 ;
provided that at least one of A or B is S;

D represents a covalent bond or CH_2 , O, S or NH;

X is CO_2R , CONR_2 , CH_2OR , $\text{P}(\text{O})(\text{OR})_2$, CONRSO_2R , SONR_2 or

10



Y is O, OH, OCOR^2 , halogen or cyano;

Z is CH_2 or a covalent bond;

- 15 R is H or R^2 ;

R^1 is H, R^2 , phenyl, or COR^2 ;

R^2 is $\text{C}_1\text{-C}_5$ lower alkyl or alkenyl;

R^3 is benzothienyl, benzofuranyl, naphthyl, or substituted derivatives thereof, wherein the substituents maybe selected from the group consisting of C_1 - C_5 alkyl, halogen, CF_3 , CN, NO_2 , NR_2 , CO_2R and OR; and R^4 is hydrogen or C_1 - C_5 alkyl.

- 5 In a still further aspect, the present invention relates to a pharmaceutical product, comprising
a container adapted to dispense its contents in a metered form; and
an ophthalmic solution therein, as hereinabove defined.

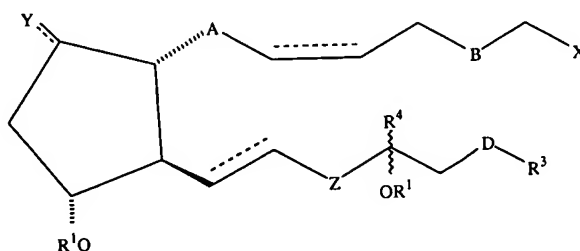
10 Brief Description of the Drawing Figures

FIG. 1 is a schematic of the chemical synthesis of a certain intermediate for the compounds of the invention as disclosed in Examples 1 through 3.

- 15 FIG. 2 is a schematic of the chemical synthesis of certain compounds related to the compounds of the invention as disclosed in Examples 4 through 7.

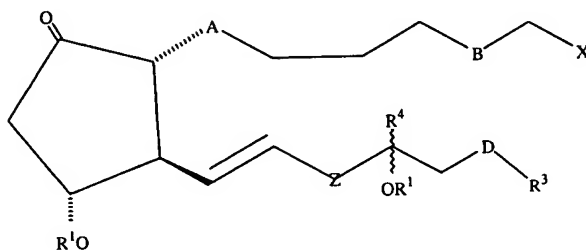
Detailed Description of the Invention

- 20 The present invention relates to the use of EP_4 agonists, e.g. 3, 7 and 3 and 7 thia or oxa prostanoid acid derivatives, as ocular hypotensives. The compounds used in accordance with the present invention are encompassed by the following structural formula I:

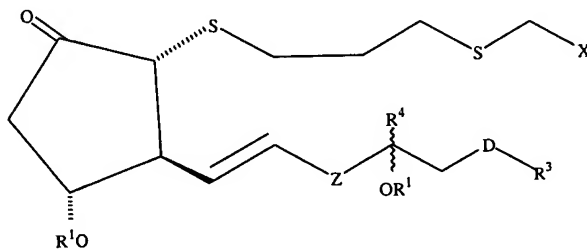


A preferred group of the compounds of the present invention includes compounds that have the following structural formula II:

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Another preferred group includes compounds having the formula III:



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In the above formulae, the substituents and symbols are as hereinabove defined.

In the above formulae:

Preferably A and B are both S.

Preferably D represents a covalent bond or is CH₂; more preferably D is CH₂.

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Preferably Z represents a covalent bond.

Preferably R is H.

Preferably R¹ is H.

Preferably R⁴ is hydrogen or methyl, most preferably hydrogen.

Preferably Y = O.

Preferably X is CO₂R and more preferably R is selected from the group consisting of H, methyl, i-propyl and n-propenyl.

The above compounds of the present invention may be prepared by methods that are known in the art or according to the working examples below. The compounds, below, are especially preferred representative, of the compounds of the present invention.

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-(hydroxy)-5-(naphthyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid methyl ester,

10

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-(hydroxy)-5-(naphthyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid,

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-(hydroxy)-5-(naphthyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid isopropyl ester,

15

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-hydroxy-5-(benzothienyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid methyl ester,

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-hydroxy-5-(benzothienyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid,

20

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-hydroxy-5-(benzothienyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid isopropyl ester,

25

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-hydroxy-5-(benzofuranyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid methyl ester,

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-hydroxy-5-(benzofuranyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid,

5 {3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-hydroxy-5-(benzofuranyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid isopropyl ester,

{3-[(1R,2S,3R)-3-Hydroxy-2-((E)-3-hydroxy-4-naphthalen-2-yl-but-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid methyl ester,

10 {3-[(1R,2S,3R)-3-Hydroxy-2-((E)-3-hydroxy-4-naphthalen-2-yl-but-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid,

{3-[(1R,2S,3R)-2-((E)-4-Benzo[b]thiophen-3-yl-3-hydroxybut-1-enyl)-3-hydroxy-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid methyl ester,

15

{3-[(1R,2S,3R)-2-((E)-4-Benzo[b]thiophen-3-yl-3-hydroxybut-1-enyl)-3-hydroxy-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid,

20 {3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-(hydroxy)-3-(methyl)-5-(naphthyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid methyl ester,

{3-[(1R,2S,3R)-3-Hydroxy-2-((E)-3-hydroxy-3-methyl-4-naphthalen-2-yl-but-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid methyl ester,

25 {3-[(1R,2S,3R)-3-Hydroxy-2-((E)-3-hydroxy-3-methyl-4-naphthalen-2-yl-but-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid,

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-(hydroxy)-3-(methyl)-5-(naphthyl)but-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid,

5 {3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-(hydroxy)-3-(methyl)-5-(benzothienyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid methyl ester and

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-(hydroxy)-3-(methyl)-5-(benzothienyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic
10 acid methyl ester.

Pharmaceutical compositions may be prepared by combining a therapeutically effective amount of at least one compound according to the present invention, or a pharmaceutically acceptable acid addition salt thereof, as an active ingredient, with conventional ophthalmically acceptable pharmaceutical excipients, and by
15 preparation of unit dosage forms suitable for topical ocular use. The therapeutically efficient amount typically is between about 0.0001 and about 5% (w/v), preferably about 0.001 to about 1.0% (w/v) in liquid formulations.

For ophthalmic application, preferably solutions are prepared using a physiological saline solution as a major vehicle. The pH of such ophthalmic solutions
20 should preferably be maintained between 6.5 and 7.2 with an appropriate buffer system. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

Preferred preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A
25 preferred surfactant is, for example, Tween 80. Likewise, various preferred vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl

cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol
5 and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

10 In a similar vein, an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

Other excipient components which may be included in the ophthalmic preparations are chelating agents. The preferred chelating agent is edentate disodium,
15 although other chelating agents may also be used in place or in conjunction with it.

The ingredients are usually used in the following amounts:

	<u>Ingredient</u>	<u>Amount (% w/v)</u>
	active ingredient	about 0.001-5
	preservative	0-0.10
20	vehicle	0-40
	tonicity adjustor	1-10
	buffer	0.01-10
	pH adjustor	q.s. pH 4.5-7.5
	antioxidant	as needed
25	surfactant	as needed
	purified water	as needed to make 100%

The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the
30 appropriate dose is well within the knowledge of the skilled artisan.

The ophthalmic formulations of the present invention are conveniently packaged in forms suitable for metered application, such as in containers equipped with a dropper, to facilitate the application to the eye. Containers suitable for

dropwise application are usually made of suitable inert, non-toxic plastic material, and generally contain between about 0.5 and about 15 ml solution.

The invention is further illustrated by the following non-limiting Examples, which are summarized in the reaction schemes of Figures 1 and 2 wherein the compounds are identified by the same designator in both the Examples and the
5 Figures.

Example 1

(R)-4-(*tert*-Butyldimethylsilanyloxy)cyclopent-2-enone (2).

10

Tetrapropylammonium perruthenate (9.4 mg, 0.027 mmol) was added to a mixture of (1S, 4R)-4-(*tert*-butyldimethylsilanyloxy)cyclopent-2-enol prepared, according to *Tetrahedron Letters*, Vol. 37, No. 18, 1996, pp. 3083-6, (118.6 mg, 0.54 mmol), 4-methylmorpholine N-oxide (94.9 mg, 0.81 mmol) and crushed 4Å
15 sieves (270 mg) in CH₂Cl₂ (10 mL). The mixture was stirred for 30 min and was passed through a plug of silica gel with CH₂Cl₂. The filtrate was concentrated *in vacuo* to give 100 mg (86%) of the above titled compound.

Example 2

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(R)-4-(*tert*-Butyldimethylsilanyloxy)-6-oxabicyclo[3.1.0]hexan-2-one (3).

Hydrogen peroxide (4.5 mL, 46.3 mmol, 30% wt. % solution in water) and 1N NaOH (46 µL, 0.046 mmol) were added to a solution of enone 2 (2.5 g, 11.5
25 mmol) in MeOH (30 mL) at 0° C. After stirring 1.5 h at 0° C the mixture was concentrated *in vacuo*, washed with saturated aqueous NH₄Cl and extracted with CH₂Cl₂ (3X). The combined organics were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford the above titled compound.

Example 3

((3-[(R)-3-(*tert*-Butyldimethylsilyloxy)-5-oxocyclopent-1-enylsulfanyl]propylsulfanyl)acetic acid methyl ester (5).

5

The epoxide **3** prepared above was diluted with CH₂Cl₂ (30 mL), (3-mercaptopropylsulfanyl) acetic acid methyl ester **4** (1.93 g, 10.7 mmol), prepared according to *Chem. Pharm. Bull.* 28 (2), 1980, 558-566, was added and the solution was cooled to 0° C. Basic alumina (11.9 g) was added and the reaction mixture was warmed to room temperature. After stirring for 18 h the mixture was filtered through celite and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, 6:1 hex/EtOAc) to yield 3.6 g (80 %) of the above titled compound.

10

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Example 4

(3-[(1R,2S,3R)-3-(*tert*-Butyldimethylsilyloxy)-2-[(S)-(E)-3-(*tert*-butyldimethylsilyloxy)oct-1-enyl]-5-oxocyclopentylsulfanyl]propylsulfanyl)acetic acid methyl ester (7).

20

tert-Butyllithium (1.47 mL of a 1.7M solution in pentane, 2.5 mmol) was added dropwise to a solution of *tert*-butyl[(S)-1-((E)-2-iodovinyl)hexyloxy]dimethylsilane **6** (462.5 mg, 1.25 mmol) in Et₂O (6.0 mL) at -78° C. After stirring for 30 min lithium 2-thienylcyanocuprate (6.0 mL of a 0.25M solution in THF, 1.5 mmol) was added and the reaction was stirred an additional 30 min at -78° C. A solution of enone **5** (430 mg, 1.1 mmol) in Et₂O (1 mL) was added and stirring was continued for an additional 1 h. The reaction mixture was then quickly poured into saturated aqueous NH₄Cl cooled to 0° C. The mixture was extracted with EtOAc and the organic portion was washed with brine, dried (Na₂SO₄), filtered and

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concentrated *in vacuo*. The residue was quickly purified by flash column chromatography (silica gel, 100% hexane followed by 8:1 hex/EtOAc) to afford 270 mg (39%) of the above titled compound.

5

Example 5

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-hydroxyoct-1-enyl)-5-oxocyclopentyl-sulfanyl]propylsulfanyl}acetic acid methyl ester (8).

10

Hydrogen fluoride-pyridine (220 μ L) was added to a solution of *bis*-TBDMS ether **7** (70 mg, 0.11 mmol) in CH₃CN (2.0 mL) at 0° C. The reaction was warmed to room temperature, stirred 1 h, and re-cooled to 0° C. The reaction was quenched with saturated aqueous NaHCO₃ until gas evolution ceased. The mixture was extracted with CH₂Cl₂ (4X). The combined organics were washed with brine, dried (Na₂SO₄),
 15 filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography (silica gel, 100% CH₂Cl₂ followed by 30:1 CH₂Cl₂:MeOH) provided 40 mg (90%) of the above titled compound.

Example 6

20

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-hydroxyoct-1-enyl)-5-oxocyclopentyl-sulfanyl]propylsulfanyl}acetic acid (9).

Methyl ester **8** (50 mg, 0.124 mmol) was dissolved in CH₃CN (10 mL) and
 25 pH 7.2 phosphate buffer (3.0 mL) was added. The mixture was treated with PLE (400 μ L, 1.34 mol/L) and stirred for 16 h at 23 °C. The reaction mixture was extracted with EtOAc (3X). The combined organics were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification of the residue by flash

column chromatography (silica gel, 100% EtOAc) gave 5.3 mg (11%) of the above titled compound.

Example 7

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{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-hydroxyoct-1-enyl)-5-oxocyclopentyl-sulfanyl]propylsulfanyl}acetic acid isopropyl ester (10).

Isopropyl-*p*-tolyltriazene (200 μ L) was added dropwise to a solution of
 10 carboxylic acid **9** (10.5 mg, 0.026 mmol) in acetone (5.0 mL) at 23 °C. After stirring
 for 1 h the reaction was quenched with 1N HCl and the solvent was removed *in*
vacuo. The residue was extracted with CH₂Cl₂ (2X). The combined organics were
 dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification of the residue by
 flash column chromatography (silica gel, 4:1 hex/EtOAc) gave 4.3 mg (38%) of the
 15 above titled compound.

Example 8

**(3-[(1R,2S,3R)-3-(*tert*-Butyldimethylsilanyloxy)-2-[(S)-(E)-3-(*tert*-
 20 butyldimethylsilanoxy)-5-(naphthyl)pent-1-enyl]-5-
 oxocyclopentylsulfanyl} propylsulfanyl)acetic acid methyl ester (H).**

**(3-[(1R,2S,3R)-3-(*tert*-Butyldimethylsilanyloxy)-2-[(S)-(E)-3-(*tert*-
 butyldimethylsilanoxy)-5-(naphthyl)pent-1-enyl]-5-
 25 oxocyclopentylsulfanyl} propylsulfanyl)acetic acid methyl ester (L).**

The named compound is prepared by substituting *tert*-butyl-[(E)-3-iodo-1-(2-naphthalen-2-yl-ethyl)allyloxy]dimethylsilane for *tert*-butyl[(S)-1-((E)-2-iodovinyl)hexyloxy]dimethylsilane in the method of Example 4. FCC gives a

higher R_f compound and a lower R_f compound, designated as H and L, respectively.

Example 9(H)

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{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-(hydroxy)-5-(naphthyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid methyl ester (H).

The named compound is prepared by repeating the method of Example 5 with the named compound of Example 8 (H) rather than the named compound of Example 4.

Example 9 (L)

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-(hydroxy)-5-(naphthyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid methyl ester (L).

15

The named compound is prepared by repeating the method of Example 5 with the named compound of Example 8 (L) rather than the named compound of Example 4.

20

Example 10 (H)

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-(hydroxy)-5-(naphthyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid (H).

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The named compound is prepared by repeating the method of Example 6 with the named compound of Example 9 (H) rather than the named compound of Example 5.

Example 10 (L)

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-(hydroxy)-5-(naphthyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid (L).

5

The named compound is prepared by repeating the method of Example 6 with the named compound of Example 9 (L) rather than the named compound of Example 5.

Example 11

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{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-(hydroxy)-5-(naphthyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid isopropyl ester.

The named compound is prepared by repeating the method of Example 7 with the named compound of Example 10 rather than the named compound of Example 6.

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Example 12

(3-[(1R,2S,3R)-3-(*tert*-Butyldimethylsilanyloxy)-2-[(S)-(E)-3-(*tert*-butyldimethylsilanoxy)-5-(benzothieryl)pent-1-enyl]-5-oxocyclopentylsulfanyl} propylsulfanyl)acetic acid methyl ester (H).

20

(3-[(1R,2S,3R)-3-(*tert*-Butyldimethylsilanyloxy)-2-[(S)-(E)-3-(*tert*-butyldimethylsilanoxy)-5-(benzothieryl)pent-1-enyl]-5-oxocyclopentylsulfanyl} propylsulfanyl)acetic acid methyl ester (L).

25

The named compound is prepared by substituting [(E)-1-(2-Benzo[*b*]thiophen-2-yl-ethyl)-3-iodoallyloxy]-*tert*-butyldimethylsilane for *tert*-

butyl[(S)-1-((E)-2-iodovinyl)hexyloxy]dimethylsilane in the method of Example 4. FCC gives a higher R_f compound and a lower R_f compound, designated as H and L, respectively.

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Example 13(H)

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-hydroxy-5-(benzothienyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid methyl ester (H).

10

The named compound is prepared by repeating the method of Example 5 with the named compound of Example 12 (H) rather than the named compound of Example 4.

Example 13(L)

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{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-hydroxy-5-(benzothienyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid methyl ester (L).

20

The named compound is prepared by repeating the method of Example 5 with the named compound of Example 12 (H) rather than the named compound of Example 4.

Example 14(H)

25

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-hydroxy-5-(benzothienyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid (H).

The named compound is prepared by repeating the method of Example 6 with the named compound of Example 13 (H) rather than the named compound of Example 5.

Example 14(L)

5

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-hydroxy-5-(benzothienyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid (L).

10 The named compound is prepared by repeating the method of Example 6 with the named compound of Example 13 (L) rather than the named compound of Example 5.

Example 15

15 **{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-hydroxy-5-(benzothienyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid isopropyl ester.**

20 The named compound is prepared by repeating the method of Example 7 with the named compound of Example 14 rather than the named compound of Example 6.

Example 16

25 **(3-[(1R,2S,3R)-3-(*tert*-Butyldimethylsilanyloxy)-2-[(S)-(E)-3-(*tert*-butyldimethylsilanyloxy)-5-(benzofuranyl)pent-1-enyl]-5-oxocyclopentylsulfanyl]propylsulfanyl)acetic acid methyl ester.**

The named compound is prepared by substituting [(E)-1-(2-Benzo[*b*]furan-2-yl-ethyl)-3-iodoallyloxy]-*tert*-butyldimethylsilane for *tert*-butyl[(S)-1-((E)-2-iodovinyl) hexyloxy]dimethylsilane in the method of Example 4.

5

Example 17

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-hydroxy-5-(benzofuranyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid methyl ester.

10

The named compound is prepared by repeating the method of Example 5 with the named compound of Example 16 rather than the named compound of Example 4.

Example 18

15 **{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-hydroxy-5-(benzofuranyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid.**

The named compound is prepared by repeating the method of Example 6 with the named compound of Example 17 rather than the named compound of Example 5.

20

Example 19

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-hydroxy-5-(benzofuranyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid isopropyl ester.

25

The named compound is prepared by repeating the method of Example 7 with the named compound of Example 18 rather than the named compound of Example 6.

Example 20

(3-[(1R,2S,3R)-3-(*tert*-Butyldimethylsilanyloxy)-2-[(E)-3-(*tert*-butyldimethylsilanoxy)-4-naphthalen-2-yl-but-1-enyl]-5-oxocyclopentylsulfanyl} propylsulfanyl)acetic acid methyl ester (H).

(3-[(1R,2S,3R)-3-(*tert*-Butyldimethylsilanyloxy)-2-[(E)-3-(*tert*-butyldimethylsilanoxy)-4-naphthalen-2-yl-but-1-enyl]-5-oxocyclopentylsulfanyl} propylsulfanyl)acetic acid methyl ester (L).

10 The named compound is prepared by substituting *tert*-butyl-((E)-3-iodo-1-naphthalen-2-yl-methylallyloxy)dimethylsilane for *tert*-butyl[(S)-1-((E)-2-iodovinyl) hexyloxy]dimethylsilane in the method of Example 4. FCC gives a higher R_f compound and a lower R_f compound, designated as H and
15 L, respectively.

Example 21 (H)

{3-[(1R,2S,3R)-3-Hydroxy-2-((E)-3-hydroxy-4-naphthalen-2-yl-but-1-enyl)-5-oxocyclopentylsulfanyl}propylsulfanyl}acetic acid methyl ester (H).

20 The named compound is prepared by repeating the method of Example 5 with the named compound of Example 20 (H) rather than the named compound of Example 4.

Example 21(L)

25 {3-[(1R,2S,3R)-3-Hydroxy-2-((E)-3-hydroxy-4-naphthalen-2-yl-but-1-enyl)-5-oxocyclopentylsulfanyl}propylsulfanyl}acetic acid methyl ester (L).

The named compound is prepared by repeating the method of Example 5 with the named compound of Example 20 (H) rather than the named compound of Example 4.

5

Example 22(H)

{3-[(1R,2S,3R)-3-Hydroxy-2-((E)-3-hydroxy-4-naphthalen-2-yl-but-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid (H).

10 The named compound is prepared by repeating the method of Example 6 with the named compound of Example 21 (H) rather than the named compound of Example 5.

Example 22(L)

15 **{3-[(1R,2S,3R)-3-Hydroxy-2-((E)-3-hydroxy-4-naphthalen-2-yl-but-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid (L).**

The named compound is prepared by repeating the method of Example 6 with the named compound of Example 21 (H) rather than the named compound of

20 Example 5.

Example 23

25 **{3-[(1R,2S,3R)-2-[(E)-4-Benzo[b]thiophen-3-yl-3-(tert-butyl)dimethylsilanyloxy]but-1-enyl]-3-(tert-butyl)dimethylsilanyloxy)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid methyl ester (H).**

{3-[(1R,2S,3R)-2-[(E)-4-Benzo[b]thiophen-3-yl-3-(*tert*-butyldimethylsilyloxy)but-1-enyl]-3-(*tert*-butyldimethylsilyloxy)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid methyl ester (L).

- 5 The named compound is prepared by substituting ((E)-1-Benzo[b]thiophen-3-ylmethyl-3-iodo-allyloxy)-*tert*-butyldimethylsilane for *tert*-butyl[(S)-1-((E)-2-iodovinyl)hexyloxy]dimethylsilane in the method of Example 4. FCC gives a higher R_f compound and a lower R_f compound, designated as H and L respectively.

10

Example 24(H)

{3-[(1R,2S,3R)-2-((E)-4-Benzo[b]thiophen-3-yl-3-hydroxybut-1-enyl)-3-hydroxy-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid methyl ester

15 (H).

The named compound is prepared by repeating the method of Example 5 with the named compound of Example 23 (H) rather than the named compound of Example 4.

20

Example 24(L)

{3-[(1R,2S,3R)-2-((E)-4-Benzo[b]thiophen-3-yl-3-hydroxybut-1-enyl)-3-hydroxy-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid methyl ester (L).

25

The named compound is prepared by repeating the method of Example 5 with the named compound of Example 23 (H) rather than the named compound of Example 4.

Example 25(H)

5 {3-[(1R,2S,3R)-2-((E)-4-Benzo[b]thiophen-3-yl-3-hydroxybut-1-enyl)-3-hydroxy-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid (H).

The named compound is prepared by repeating the method of Example 6 with the named compound of Example 24 (H) rather than the named compound of Example 5.

10

Example 25(L)

15 {3-[(1R,2S,3R)-2-((E)-4-Benzo[b]thiophen-3-yl-3-hydroxybut-1-enyl)-3-hydroxy-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid (L).

15

The named compound is prepared by repeating the method of Example 6 with the named compound of Example 24 (H) rather than the named compound of Example 5.

20

Example 26

(3-[(1R,2S,3R)-3-(*tert*-Butyldimethylsilanyloxy)-2-[(S)-(E)-3-(*tert*-butyldimethylsilanoxy)-3-(methyl)-5-(naphthyl)pent-1-enyl]-5-oxocyclopentylsulfanyl] propylsulfanyl)acetic acid methyl ester (H).

25 (3-[(1R,2S,3R)-3-(*tert*-Butyldimethylsilanyloxy)-2-[(S)-(E)-3-(*tert*-butyldimethylsilanoxy)-3-(methyl)-5-(naphthyl)pent-1-enyl]-5-oxocyclopentylsulfanyl] propylsulfanyl)acetic acid methyl ester (L).

The named compound is prepared by substituting *tert*-Butyl-[(E)-3-iodo-1-methyl-1-(2-naphthalen-2-yl-ethyl)allyloxy]dimethylsilane for *tert*-butyl[(S)-1-((E)-2-iodovinyl)hexyloxy]dimethylsilane in the method of Example 4. FCC gives a higher R_f compound and a lower R_f compound, designated as H and L,

5 respectively.

Example 27(H)

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-(hydroxy)-3-(methyl)-5-(naphthyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic
10 acid methyl ester (H).

The named compound is prepared by repeating the method of Example 5 with the named compound of Example 26 (H) rather than the named compound of Example 4.

15

Example 27(L)

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-(hydroxy)-3-(methyl)-5-(naphthyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic
20 acid methyl ester (L).

The named compound is prepared by repeating the method of Example 5 with the named compound of Example 26 (H) rather than the named compound of Example 4.

25

Example 28(H)

5 {3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-(hydroxy)-3-(methyl)-5-(naphthyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid (H).

The named compound is prepared by repeating the method of Example 6 with the named compound of Example 27 (H) rather than the named compound of Example 5.

10 Example 28(L)

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-(hydroxy)-3-(methyl)-5-(naphthyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid (L).

15 The named compound is prepared by repeating the method of Example 6 with the named compound of Example 27(L) rather than the named compound of Example 5.

20 Example 29

(3-[(1R,2S,3R)-3-(*tert*-Butyldimethylsilanyloxy)-2-[(E)-3-(*tert*-butyldimethylsilanoxy)-3-methyl-4-naphthalen-2-yl-but-1-enyl]-5-oxocyclopentylsulfanyl] propylsulfanyl)acetic acid methyl ester (H).

25 (3-[(1R,2S,3R)-3-(*tert*-Butyldimethylsilanyloxy)-2-[(E)-3-(*tert*-butyldimethylsilanoxy)-3-methyl-4-naphthalen-2-yl-but-1-enyl]-5-oxocyclopentylsulfanyl] propylsulfanyl)acetic acid methyl ester (L).

The named compound is prepared by substituting *tert*-butyl-[(E)-3-iodo-1-methyl-1-(2-naphthalen-2-yl-methyl)allyloxy]dimethylsilane for *tert*-butyl[(S)-1-((E)-2-iodovinyl) hexyloxy]dimethylsilane in the method of Example 4. FCC gives a higher R_f compound and a lower R_f compound, designated as H and L, respectively.

Example 30(H)

{3-[(1R,2S,3R)-3-Hydroxy-2-((E)-3-hydroxy-3-methyl-4-naphthalen-2-yl-but-1-enyl)-5-oxocyclopentylsulfanyl}propylsulfanyl}acetic acid methyl ester
(H).

The named compound is prepared by repeating the method of Example 5 with the named compound of Example 29 (H) rather than the named compound of Example 4.

Example 30(L)

{3-[(1R,2S,3R)-3-Hydroxy-2-((E)-3-hydroxy-3-methyl-4-naphthalen-2-yl-but-1-enyl)-5-oxocyclopentylsulfanyl}propylsulfanyl}acetic acid methyl ester
(L).

The named compound is prepared by repeating the method of Example 5 with the named compound of Example 29 (L) rather than the named compound of Example 4.

Example 31(H)

{3-[(1R,2S,3R)-3-Hydroxy-2-((E)-3-hydroxy-3-methyl-4-naphthalen-2-yl-but-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid (H).

5

The named compound is prepared by repeating the method of Example 6 with the named compound of Example 30 (H) rather than the named compound of Example 5.

Example 31(L)

10

{3-[(1R,2S,3R)-3-Hydroxy-2-((E)-3-hydroxy-3-methyl-4-naphthalen-2-yl-but-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid (L).

15

The named compound is prepared by repeating the method of Example 6 with the named compound of Example 30 (L) rather than the named compound of Example 5.

Example 32

20

(3-[(1R,2S,3R)-3-(*tert*-Butyldimethylsilyloxy)-2-[(S)-(E)-3-(*tert*-butyldimethylsilyloxy)-3-(methyl)-5-(benzylthienyl)pent-1-enyl]-5-oxocyclopentylsulfanyl] propylsulfanyl)acetic acid methyl ester (H).

25

(3-[(1R,2S,3R)-3-(*tert*-Butyldimethylsilyloxy)-2-[(S)-(E)-3-(*tert*-butyldimethylsilyloxy)-3-(methyl)-5-(benzothienyl)pent-1-enyl]-5-oxocyclopentylsulfanyl] propylsulfanyl)acetic acid methyl ester (L).

The named compound is prepared by [(E)-1-(2-Benzo[*b*]thiophen-2-yl-ethyl)-3-iodo-1-methylallyloxy]-*tert*-butyldimethylsilane for *tert*-butyl[(S)-1-((E)-2-

iodovinyl) hexyloxy]dimethylsilane in the method of Example 4. FCC gives a higher R_f compound and a lower R_f compound, designated as H and L, respectively.

Example 33(H)

5

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-(hydroxy)-3-(methyl)-5-(benzothienyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid methyl ester (H).

10 The named compound is prepared by repeating the method of Example 5 with the named compound of Example 32 (H) rather than the named compound of Example 4.

Example 33(L)

15 **{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-(hydroxy)-3-(methyl)-5-(benzothienyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid methyl ester (L).**

20 The named compound is prepared by repeating the method of Example 5 with the named compound of Example 32 (L) rather than the named compound of Example 4.

Example 34(H)

25 **{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-(hydroxy)-3-(methyl)-5-(benzothienyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid (H).**

The named compound is prepared by repeating the method of Example 6 with the named compound of Example 33 (H) rather than the named compound of Example 5.

Example 34(L)

5

{3-[(1R,2S,3R)-3-Hydroxy-2-((S)-(E)-3-(hydroxy)-3-(methyl)-5-(benzothienyl)pent-1-enyl)-5-oxocyclopentylsulfanyl]propylsulfanyl}acetic acid (L).

10

The named compound is prepared by repeating the method of Example 6 with the named compound of Example 33L rather than the named compound of Example 5.

15

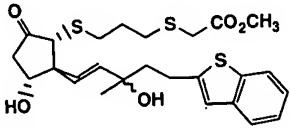
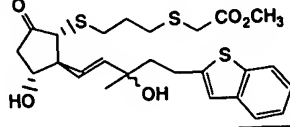
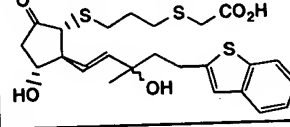
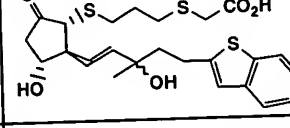
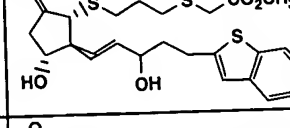
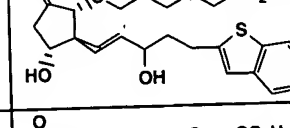
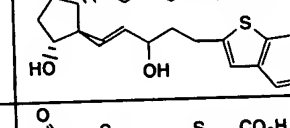
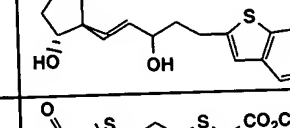
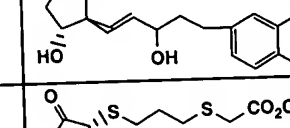
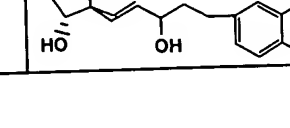
The effects of the compounds of this invention on intraocular pressure may be measured as follows. The compounds are prepared at the desired concentrations in a vehicle comprising 0.1% polysorbate 80 and 10 mM TRIS base. Dogs are treated by administering 25 μ l to the ocular surface, the contralateral eye receives vehicle as a control. Intraocular pressure is measured by applanation pneumatonometry. Dog intraocular pressure is measured immediately before drug administration and at 6 hours thereafter.

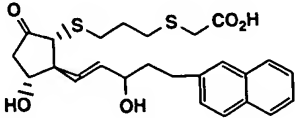
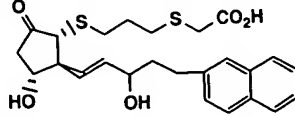
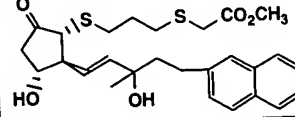
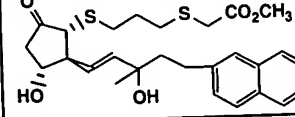
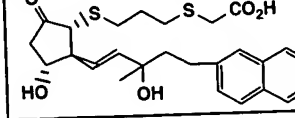
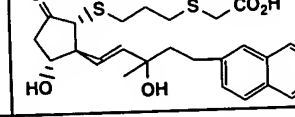
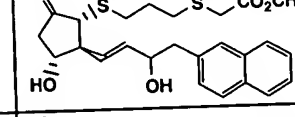
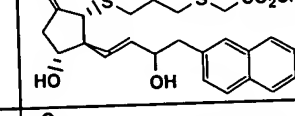
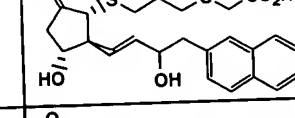
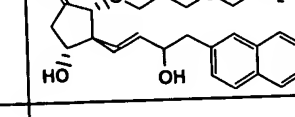
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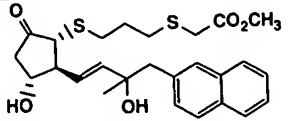
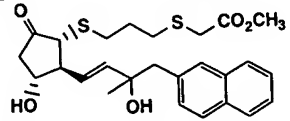
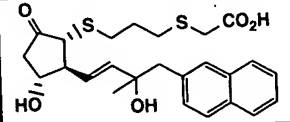
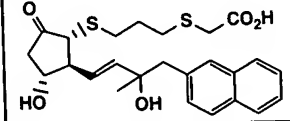
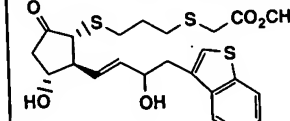
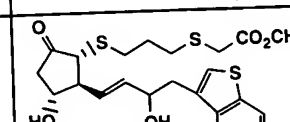
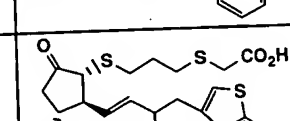
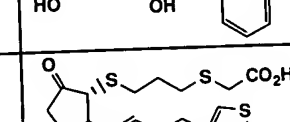
The compounds of Examples 9H, 9L, 10H, 10L, 13H, 13L, 14H, 14L, 21H, 21L, 22H, 22L, 24H, 25H, 25L, 27H, 27L, 28H, 28L, 30H, 30L, 31H, 31L, 33H, 33L, 34H and 34L are useful in lowering elevated intraocular pressure in mammals, e.g. humans.

25

The compounds of the Examples are subject to *in vitro* testing as described below. The results are reported in the table.

Example No.		hEP ₄
33H		200
33L		300
34H		32
34L		68
13H		91
13L		93
14H		27
14L		13
9H		40
9L		40

Example No.		hEP ₄
10H		450
10L		19.5
27H		500
27L		3400
28H		1700
28L		1500
21H		100
21L		13
22H		32
22L		6.2

Example No.		hEP ₄
30H		3100
30L		3200
31H		300
31L		900
24H		200
24L		30
25H		69
25L		5

HUMAN RECOMBINANT EP₄ RECEPTOR: STABLE TRANSFECTANTS.

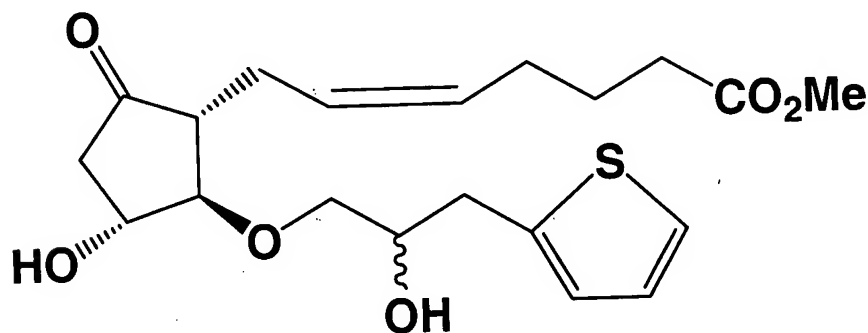
Plasmids encoding the human EP₄ receptor were prepared by cloning the
 5 respective coding sequences into the eukaryotic expression vector pCEP4
 (Invitrogen). The pCEP4 vector contains an Epstein Barr virus (EBV) origin of

replication, which permits episomal replication in primate cell lines expressing EBV nuclear antigen (EBNA-1). It also contains a hygromycin resistance gene that is used for eukaryotic selection. The cells employed for stable transfection were human embryonic kidney cells (HEK-293) that were transfected with and express the EBNA-1 protein. These HEK-293-EBNA cells (Invitrogen) were grown in medium containing Geneticin (G418) to maintain expression of the EBNA-1 protein. HEK-293 cells were grown in DMEM with 10% fetal bovine serum (FBS), 250 $\mu\text{g ml}^{-1}$ G418 (Life Technologies) and 200 $\mu\text{g ml}^{-1}$ gentamicin or penicillin/streptomycin. Selection of stable transfectants was achieved with 200 $\mu\text{g ml}^{-1}$ hygromycin, the optimal concentration being determined by previous hygromycin kill curve studies.

For transfection, the cells were grown to 50-60% confluency on 10 cm plates. The plasmid pCEP4 incorporating cDNA inserts for the respective human prostanoid receptor (20 μg) was added to 500 μl of 250 mM CaCl_2 . HEPES buffered saline x 2 (2 x HBS, 280 mM NaCl, 20 mM HEPES acid, 1.5 mM Na_2HPO_4 , pH 7.05 – 7.12) was then added dropwise to a total of 500 μl , with continuous vortexing at room temperature. After 30 min, 9 ml DMEM were added to the mixture. The DNA/DMEM/calcium phosphate mixture was then added to the cells, which had been previously rinsed with 10 ml PBS. The cells were then incubated for 5 hr at 37° C in humidified 95% air/5% CO_2 . The calcium phosphate solution was then removed and the cells were treated with 10% glycerol in DMEM for 2 min. The glycerol solution was then replaced by DMEM with 10% FBS. The cells were incubated overnight and the medium was replaced by DMEM/10% FBS containing 250 $\mu\text{g ml}^{-1}$ G418 and penicillin/streptomycin. The following day hygromycin B was added to a final concentration of 200 $\mu\text{g ml}^{-1}$.

Ten days after transfection, hygromycin B resistant clones were individually selected and transferred to a separate well on a 24 well plate. At confluence each clone was transferred to one well of a 6 well plate, and then expanded in a 10 cm dish. Cells were maintained under continuous hygromycin selection until use.

The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. However, it is apparent for one of ordinary skill in the art that further compounds with the desired pharmacological properties can be prepared in an analogous manner, and that the disclosed compounds can also be obtained from different starting compounds via different chemical reactions. Similarly, different pharmaceutical compositions may be prepared and used with substantially the same result. For example, the EP4 agonists disclosed and claimed U.S. Patent No. 6,410,591 B1, which is hereby incorporated by reference may be used in the method of the present invention. In addition, GR 50209X, a receptor selective EP₄-receptor agonist, may also be used in the method of the present invention. (GR 50209X has the following structure:



Thus, however detailed the foregoing may appear in text, it should not be construed as limiting the overall scope hereof; rather, the ambit of the present invention is to be governed only by the lawful construction of the appended claims.